REMARKS

Claims 1-9 and 11-28 currently appear in this application. The Office Action of February 27, 2002, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicants respectfully request favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Rejections under 35 U.S.C. 112

Claims 1-3, 5-13 and 15-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is said to have a limitation written inside parentheses, which renders the claim indefinite.

This rejection is respectfully traversed. It is believed that the Examiner is really objecting to the material contained within brackets, which has traditionally been an instruction to delete that material. The brackets have been deleted. However, it is respectfully submitted that the parentheses are necessary to define the invention. The molar ratio of (a+b) to c is a limitation in the claim. This means that the molar ratio of the amount of a plus the amount of b

has a ratio to c of the sum of a + b should be in parentheses to make it clear that it is the sum of these two components that bears a molar relationship to c; otherwise, it is not clear whether it is a and b, or b alone, which bears that molar relationship to c.

Claim 10 has been cancelled by the present amendment.

Art Rejections

Claim 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by any of Holmes-Farley et al. 5,496,545, 6,083,495 or 5,687,775, the three specifications being almost identical.

This rejection is respectfully traversed. The present invention is directed to a phosphate-binding polymer represented by the formula in claim 1 and which has a true specific gravity of 1.18-1.24 (claim 1) and preferably a specific gravity of 1.20-1.22 (claim 2). From the formula of claim 1, it can readily be seen that the polymer is a polyallylamine crosslinked with epichlorohydrin. However, the inventors have confirmed that a crosslinked polyallylamine having a true specific gravity of 1.18-1.24 cannot be prepared by a crosslinking reaction using water as a reaction medium. The specification as filed at page 6, lines 22-27, and "Preparation 2" on page 12, lines 18-28 makes it clear

that water cannot be used as a reaction medium to prepare. Preparation 2 clearly discloses that using water as a crosslinking reaction medium produced a polymer having a true specific gravity of 1.253, which is well outside the range of true specific gravity of the present invention.

Submitted herewith is the declaration of Katsuya MATSUDA, one of the inventors of the present application, which demonstrates that there is a relationship between the methods of preparing phosphate-binding polymers and the specific gravity of these polymers. It is clear from this declaration that polymers crosslinked using water have a much higher true specific gravity than do polymers crosslinked using a mixture of water and acetonitrile.

Holmes, on the other hand, discloses phosphate binding polymers which are useful for removing phosphate from the gastrointestinal tract. Holmes discloses that the polymer may be crosslinked using a crosslinking agent. However, polyallylamine/epichlorohydrin, which corresponds to the polymer defined by claim 1 of the present application, was produced by reacting polyallylamine with epichlorohydrin in water. Thus, the polymers of Holmes are **not** the same as the polymers of the present invention, which are crosslinked in

water/acetonitrile. There is nothing in Holmes which teaches or suggests the use of a water/acetonitrile medium for the crosslinking reaction. Attention is directed to the top of column 8, lines 15-33 of Holmes.

Accordingly, it is respectfully submitted that Holmes has not produced a polyallylamine crosslinked with epichlorohydrin having a true specific gravity of 1.18 to 1.24. The differences in true specific gravity are directly related to the medium in which the crosslinking is effected. Therefore, it is respectfully submitted that none of the Holmes or Holmes-Farley patents anticipates the herein claimed invention.

Claims 1-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of the Holmes patents discussed above and in view of the Examiner's comments. The Examiner admits that Holmes does not teach the specific gravity ranges claimed by applicant. The Examiner further concedes that Holmes does not specifically teach a particle size for the polymer once it is incorporated into the tablet formulation. The Examiner alleges that Holmes teaches that the polymeric phosphate binder may be mixed with, diluted by, or enclosed within a carrier, without disclosing a specific carrier. Holmes allegedly claims the method of making

the pharmaceutical composition by crosslinking the polymer and mixing the polymer with a carrier.

This rejection is respectfully traversed. The polymers of the present invention have a specific gravity of 1.18 to 1.24, which are not disclosed or suggested by any of the Holmes or farley-Farley patents. Additionally, polymers of the present invention exhibit unexpectedly superior effects in preparing tables as compared to the polymers described in Holmes and Holmes-Farley.

While claim 10 recited the polymer used was the polymer disclosed in Holmes, it should be noted that claim 10 depends from claim 4, which recites that the polymer has a specific gravity of 1.18 to 1.24. That is, the polymer recited in claim 10 was a crosslinked polyallylamine, as are the polymers disclosed in Holmes, but the polymers in the present invention are prepared by crosslinking in water/acetonitrile rather than in water, which produces polymers having a different specific gravity. Thus, the polymers of the present invention are **not** the same as the polymers of Holmes.

The specific gravity of the polymers makes a difference in tablets prepared from these polymers. As described in Example 1, particularly Table 1 of the present application on page 13, the polymers of the

present invention can produce tablets having a desirable hardness of more than 6.0 KP. It is clear from Table 1 that none of the tables prepared from a phosphate-binding polymer with a true specific gravity of 1.253 had adequate hardness. However, tablets prepared from phosphate-binding polymers having true specific gravities of 1.209-1.211 had adequate hardness when compressed at pressures of 1000 kg or more.

The phosphate-binding polymers are taken in a relatively large single dose, *i.e.*, from 1 to 2 grams. The phosphate-binding polymers cannot be taken *per se*, because they react with water and rapidly swell. In order to make administration easy for patients, it is desirable and necessary that the tablets be reduced in size by means of compression, and that tablets be coated with a thin film to prevent disintegration in the mouth and enable easy ingestion.

In addition, patients who require administration of phosphate-binding polymers to treat hyperphosphatemia are usually undergoing dialysis. Thus, these patients are often required to ingest limited amounts of water, and therefore, the dosage forms of phosphate-binding polymer are to be taken only with a small amount of water. This is described in the

specification as filed at page 3, line 21 to page 4, line 11.

As explained above, the tablets must be coated with a film in order to ease administration. Uncoated tablets should have a sufficient hardness, *i.e.*, in excess of 6 KP, and have a maximum weight loss of not more than 1%. Submitted herewith is a copy of 2000, *The United States Pharmacopoeia (USP)*, 24, NF 19 (1216), Tablet Friability, pages 2148-2149. The hardness and maximum weight loss of uncoated tablets are stipulated in this manual.

If the uncoated tablets are insufficiently hard or have an undesirably high maximum weight loss, the coated tablets will have a rough surface, which limits their application and therefore their market value. These problems can be solved by using a relatively large amount of an excipient such as crystalline cellulose and/or low substituted hydroxypropyl cellulose. However, the use of a large amount of excipient increase the size of the tablets and makes them more difficult to administer. Thus, a phosphate-binding polymer which is capable of being formulated with a small amount of or no excipient to uncoated tablets having a sufficient hardness and a low maximum loss of weight is particularly desirable.

According to the present invention, a polymer which has a certain range of true specific gravity and which exhibits the desired physical properties of sufficient hardness and minimum weight loss has been provided. This polymer, which has a true specific gravity of 1.18-1.24, is produced by crosslinking the polymer in water/acetonitrile, and thus is a very different polymer from those produced by crosslinking in water alone.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK
Attorneys for Applicant(s)

By: _____
Anne M. Kornbau
Reg. No. 25,884

624 Ninth Street, N.W., Suite 300
Washington, D.C. 20001-5303
Telephone: (202)628-5197
Facsimile: (202)737-3528
AMK:nmp
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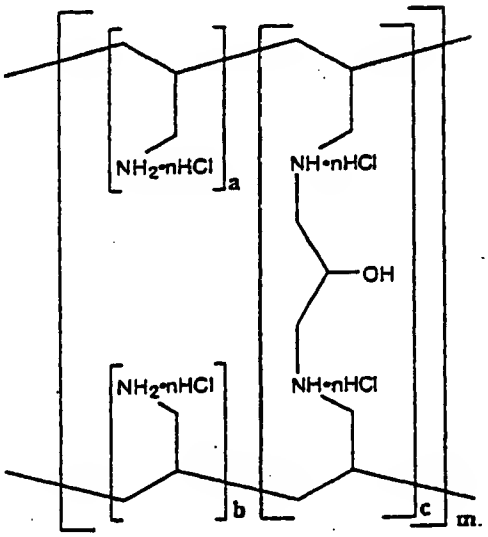
"Version with markings to show changes"

1. (Amended) A phosphate-binding polymer that is represented by the formula



~~[~~where the molar ratio of (a+b) to c is form 45:1 to 2:1 and m is an integer~~]~~ and which has a true specific gravity of 1.18-1.24.